Microbial Keratitis/Corneal Ulceration
QEI Spring 2007 Newsletter
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Microbial keratitis, particularly bacterial, is the most common serious ocular infection that primary eye care doctors encounter and may be caused by a variety of bacteria, viruses, and parasites. Immediate diagnosis and subsequent treatment are critical to avoiding potentially vision threatening sequellae, such as corneal scarring or perforation. This newsletter will emphasize the diagnosis and management of bacterial corneal ulcerations.

Clinical symptoms and signs:

- Symptoms: Mild to severe ocular pain, photophobia, decreased vision, tearing, and discharge.
- Signs:
  - Mild to severe conjunctival inflammation, focal white opacity in the corneal stroma (infiltrate), staining of the area (indicating a corneal ulcer), corneal thinning, stromal edema, folds in Descemet's membrane, mild to severe (hypopyon) anterior chamber reaction, and eyelid edema.

Differential diagnosis:

- Infection: bacterial, fungal, Acanthamoeba, viral/HSV
- CLARE: Contact Lens Acute Red Eye
- CLPU: Contact Lens-Induced Peripheral Ulcer
- Infiltrates in contact lens wear
- Fungal & Acanthamoeba infection
- Staph hypersensitivity ulceration
- EKC: Epidemic Keratoconjunctivitis
- HSV: Herpes Simplex Virus
- Immune-mediated corneal infiltrates
- Toxic-related corneal infiltrates
- Foreign body

Bacterial corneal ulcerations are the most common form of corneal ulceration. In general, patients will present with decreased vision, swift onset of pain, photophobia, conjunctival injection, and anterior segment inflammation. A variety of microorganisms on the eyelids and ocular surface continually provide a source for microbial keratitis. Though the intact cornea can prevent many infections, bacteria such as Neisseria gonorrhoeae, Listeria, Corynebacterium, and Haemophilus aegypticus can penetrate an intact cornea. The most common bacteria found associated with corneal ulcerations are Staphylococcus, Streptococcus, Pseudomonas, and Moraxella. Risk factors for microbial keratitis include contact lens wear (especially extended wear), pre-existing ocular surface disease, older age, corneal injury/surgery, contaminated meds, and systemic history.

Cultures and Staining: Cultures tend to be positive 40-45%.

When in doubt of the diagnosis or etiology, culture.

Indications that may warrant culturing:

- size: infiltrate with > 2mm epithelial defect
- location: infiltrate > 2 mm from the limbus
- depth: infiltrate > 20% of the corneal thickness
- associated findings: anterior chamber reaction > grade 2
- organic trauma
- atypical ulcerations: younger individuals and children
- unresponsive ulcers w/in 24 hrs

- immunocompromised patients
- hospitalized patients or hospital staff

Culture Media:

- Sabourad's agar: fungi at room temperature
- chocolate agar: Haemophilus and Gonococcus in a CO2 jar
- blood agar: most bacteria especially the Staphylococcus and Streptococcus
- thioglycolate broth: - transport media for aerobic and anaerobic bacteria
  - transport for ulcers already treated

Optional cultures:

- Lowenstein-Jensen medium: Mycobacteria and Nocardia
- non-nutrient agar with E. coli overlay: Acanthamoeba

Staining Techniques:

gram staining: bacteria and fungi (may guide initial treatment)
giemsa staining: bacteria, fungi, and Acanthamoeba

Optional staining techniques:

- gomori methenamine-silver, PAS: fungi
- acid-fast: Mycobacteria and Nocardia
- calcofluor white: Acanthamoeba

Culture Technique:

- scrapings deep from the base of the ulcer or the leading edge are essential
- Kimura spatula works well for corneal and conjunctival scrapings
- cotton swab may be used to retrieve material from the conjunctival fornices

Treatment:

Therapy for bacterial corneal ulceration has changed and evolved with the advent of the fluoroquinolones (Ciloxan and Ocuflox). Prior treatment had been with specially made fortified antibiotics of aminoglycosides and cefazolin; these were difficult to prepare and many pharmacies did not prepare. Fluoroquinolones have been shown to be as effective in treating corneal ulcerations as these prepared fortified antibiotics: 95% fluoroquinolones vs 93% fortified antibiotics. Currently the only two commercially FDA approved therapies for bacterial corneal ulceration are Ocuflox and Ciloxan. However, with the new fourth generation fluoroquinolones we have additional options for our corneal ulcer patients. These meds inhibit **topoisomerase II,** which is found primarily in gram(-) bacteria **and topoisomerase IV**, which predominates in gram(+) bacteria These meds, though not FDA approved for treatment of bacterial corneal ulceration, have become the standard of care for clinical, empirical bacterial corneal ulcer therapy.

Evolution of the Fluoroquinolones: see Table 1:

Much confusion exists about the evolution of the fluoroquinolones. Naldixic acid, 1962, was created as a byproduct of chloroquine synthesis. Naldixic acid was found to inhibit an enzyme critical for bacterial synthesis, topoisomerase II, DNA gyrase. This product had limited use and was mostly effective against gram negative bacteria.

In the 1980s, the second generation agents were introduced orally and had a 1000 fold greater affect on gram negative species with enhanced activity against staphylococci and streptococci. The topical forms, Ciloxan and Ocuflox, followed in the 1990s.

The second/third generation agents, such as Quixin, are classified in this manner based upon mechanism action (inhibition of topoisomerase II and some inhibition of topoisomerase IV) and timing to market.

The fourth generations were introduced orally in the 1990s and had improved gram(+) effectivity especially against pneumococcal and penicillin-resistant organisms. Topically these agents hit the market in the early 2000s as Zymar and Vigamox. These agents have both topoisomerase II-gram(-) and topoisomerase IV-gram(+) activity and are the most recently released topical fluoroquinolones. By inhibiting two enzymes, bacteria now need to go through two mutations for resistance making, therefore making resistance development more difficult. The increased gram(+) activity is very important since 60%-70% of ocular flora are gram(+).

Resistance, prophylaxis, as well as other antibiotics and uses will not be discussed in this newsletter. We advise the clinician to evaluate the literature to make choices for antibiotic therapy for conditions other than bacterial corneal ulcers.

(Please read below for more clinical details for each drug.)

Table 1:

1st Generation	2nd Generation	3rd Generation	4th Generation
Naldixic Acid	Norfloxacin	Sparfloxacin	Gatafloxacin
	Lomefloxacin	Grepafloxacin	Moxifloxacin
	Ciprofloxacin	Levofloxacin	
	Ofloxacin		

Fluoroquinolones:

Ciloxan: 0.3% Ciprofloxacin HCl Sterile Ophthalmic Solution and Ointment

- FDA approved for ulcer bacterial corneal ulcer therapy.
- Preservative: .006% BAK.
- pH: 4.5.
- Osmolality: 300mOsm.
- Bactericidal mechanism: interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA.
- Clinical comment:
  - Increased resistance by gram positive organisms.
  - Very good for gram negative and Pseudomonas.
  - White crystalline precipitate located superficially in the corneal defect when dosed at high levels. This will resolve over time as the drug is reduced to q.i.d. dosage. No adverse findings were found due to the precipitate.
  - Very effective against gram negative bacteria and pseudomonas.
  - Very limited activity against gram positive organisms.
  - Increased resistance due to single mechanism of enzyme inhibition.
- Pregnancy category: C.
- Pediatric use: > 1 year of age.
- Dosage:
  - Conjunctivitis: 1-2 drops q 2 h x 2 days, then q.i.d. x 5 days.
  - Keratitis/ulceration: see below for ulceration dosage.

Ocuflox: 0.3% Ofloxacin Sterile Ophthalmic Solution

- FDA approved for bacterial corneal ulcer therapy
- Preservative: .005% BAK.
- pH: 6.4.
- Osmolality: 300 mOsm.
- Bactericidal mechanism: interference with the enzyme DNA gyrase.
- Clinical Comment:
  - Very effective against gram negative bacteria with limited effectiveness for gram positives.
  - Increased resistance to gram + and – organisms.
  - pH is better tolerated with no precipitate formation.
- Pregnancy category: C.
- Pediatric use: > 1 year of age.
- Dosage:
  - Conjunctivitis: 1-2 drops q 2-4h x 2 days, then q.i.d. x 5 days.
  - Keratitis/ulceration: see below for ulceration dosage.

Quixin: 0.5% Levofloxacin Sterile Ophthalmic Solution

- FDA approved for bacterial conjunctivitis.
- L-isomer of oflaoxacin.
- Preservative: .005% BAK.
- pH: 6.5.
- Osmolality: 300 mOsm.
- Bactericidal mechanism: inhibition of DNA gyrase and limited inhibition of topoismoerase IV.
- Clinical Comment:
  - Classified as third generation due to inhibition of topoisomerase II and IV and timing to the market place for clinical use.
  - Inhibition of topoisomerase IV is limited and not as effective as the fourth generation agents.
- Pregnancy category: C
- Pediatric use: >1 year of age
- Dosage: see below
  - Conjunctivitis: 1-2 drops q 2h x 2 days, then q.i.d. x 5 days.
  - Keratitis/ulceration: see below for ulceration dosage.

Zymar: 0.3% Gatifloxacin Sterile Ophthalmic Solution

- FDA approved for the treatment of bacterial conjunctivitis.
- Preservative: .005% BAK.
- pH: 6.
- Osmolality: 260-330 mOsm.
- Bactericidal mechanism: inhibition of DNA gyrase (II) and topoisomerase IV.
- Clinical Comment:
  - This generation has added a new C-8 methoxyl group.
  - Contains BAK, thus providing an additive effect in the kill of bacteria.
  - Larger bottle size.
- Pregnancy category: C.
- Pediatric use: > 1year of age.
- Dosage:
  - Conjunctivitis: 1 drop q 2h x 2 days, then q.i.d. x 5 days.
  - Keratitis/ulceration: see below for ulceration dosage.

Vigamox: 0.5% Moxifloxacin HCL Sterile Ophthalmic Solution

- FDA approved for the treatment of bacterial conjunctivitis.
- Preservative: none.
- pH: 6.8.
- Osmolality: 290 mOsm.
- Bactericidal mechanism: inhibition of DNA gyrase (II) and topisomerase IV.
- Clinical Comment:
  - This generation has added a new C-8 methoxyl group.
  - Bulky C-7 side chain to prevent efflux out of the bacterial cell: enhancing kill and preventing resistance.
  - Non-preserved compound, more neutral pH, 0.5% concentration, t.i.d. dosing for bacterial conjunctivitis.
- Pregnancy category: C.
- Pediatric use: > 1 year of age.
- Dosage:

- Conjunctivitis: 1 drop t.i.d. for x 7 days.
- Keratitis/ulceration: see below for ulceration dosage.

Dosage:

- **Loading Dose:** Dosing is very frequent for the first 24 to 48 hours, with dosing higher and more frequent as severity dictates. Meds can be tapered as the patient responds to therapy, however antibiotics should never be tapered below there recommended FDA dosages, which is typically q.i.d. Below is a guideline that can be applied generally with the therapy of bacterial corneal ulcers. The clinician needs to assess the severity and apply judgment to the appropriate dosing and taper.

  Initial Therapy:
  - 1 drop q 5 minutes x 30 minutes, followed by every 30 minutes x 2-6 hours.
  - Dosing may be reduced to 1 drop every hour while awake with an antibiotic ointment at bedtime, or drops may be continued through the night as severity dictates.
  - **Severe cases:** use drops as directed through the night. Consider addition of oral **doxycycline/tetracycline** therapy due to its anti-inflammatory properties and inhibition of collagenalytic activity within the cornea. Inhibits Metalloproteinase-9 activity and thus the inflammatory cascade.
  - **Less severe cases:** use tobramycin: gram(-), or bacitracin: gram(+) ointment at bedtime instead of drops through the night.
  - **Cycloplegia:** This is done to minimize secondary inflammation and help ciliary muscle spasm. The patient should de adequately dilated first with 1% tropicamide and 2.5% phenylephrine to achieve a good dilation. This will help the cycloplegic agent to take better effect. **Less severe cases** may need 1-2 drops of 5% homatropine in the office after dilation versus in **more severe cases** 5% homatropine is dispensed at b.i.d. to t.i.d. dosing.
  - **Reevaluate daily** until the appropriate response occurs. Appropriate response at the first follow-up is a subjective improvement, especially in pain and/or less rapid progression of infection by slit lamp exam. Days 2-6, the clinician should see the beginning of resolution of the clinical signs.

  Day 1 Follow-up:
  - 1 drop q 1 hour while awake.
  - 1 drop q 2h after bedtime vs antibiotic ointment at bedtime.

  Days 2-6:
  - 1 drop q2h while awake.
  - 1 drop q 4 h after bedtime vs antibiotic ointment.

  Days 7-21:
  - 1 drop q.i.d. while awake and continue as long as appropriate.
  - D/C pills and ointment as appropriate.

  Topical steroids:
  - Should be used cautiously!! Topical steroids are used in attempt to decrease corneal scarring after the epithelium is healing and the inflammation is resolving. We would recommend q.i.d. dosing of prednisolone when deemed appropriate.

  Follow-up
  - Every 2-5 days after initial improvement is seen.

- Re-educate the patient to the etiology may aid in decreasing the recurrence rate.
    - i.e. proper contact lens care and wear
- Pseudomonas ulcers tend to recur unless totally sterilized.